



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07F 9/40, A61K 31/66</p>	<p>A1</p>	<p>(11) International Publication Number: WO 93/12123 (43) International Publication Date: 24 June 1993 (24.06.93)</p>
<p>(21) International Application Number: PCT/GB92/02226 (22) International Filing Date: 1 December 1992 (01.12.92) (30) Priority data: 9126144.6 10 December 1991 (10.12.91) GB (71) Applicant (for all designated States except US): BRITISH BIO-TECHNOLOGY LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): LEWIS, Christopher, Norman [GB/GB]; DAVIDSON, Alan, Hornsby [GB/GB]; ALLANSON, Nigel, Mark [GB/GB]; British Bio-technology Ltd, Watlington Road, Cowley, Oxford OX4 5LY (GB).</p>		<p>(74) Agent: WALLS, Alan, James; British Bio-Technology Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). (81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.</p>
<p>(54) Title: 3-CARBOXY-2-HYDROXY-PROPANE-PHOSPHONIC ACID DERIVATIVES</p> <div data-bbox="565 1234 1084 1558" data-label="Chemical-Block"> <p style="text-align: right;">(I)</p> </div> <p>(57) Abstract</p> <p>Compounds of general formula (I), wherein R₁ represents a C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl(C₁₋₈)alkyl, C₂₋₈ alkenyl, optionally C₁₋₆ alkyl substituted phenyl, or optionally substituted phenyl(C₁₋₆ alkyl) group; R₂ represents C₁₋₈ alkyl group; R₃ represents a C₂₋₆ alkenyl group or a C₂₋₆ alkenyl group linked to an optionally substituted phenyl group; R₄ represents a hydrogen atom, a C₁₋₅ alkyl group, a C₁₋₅ alkyl group substituted with a group chosen from optionally substituted phenyl, dimethylamino or acetyl amino; or a group M; R₅ represents a hydroxyl, -OM, or a C₁₋₈ alkoxy group; M represents a cation capable of forming a pharmaceutically acceptable salt; X represents an oxygen atom, NH group or CH₂ group; a, b and c represent independently single or double bonds except that when a or c are double bonds then b represents a single bond; or pharmaceutically or veterinarily acceptable acid addition salts or hydrates thereof are potent inhibitors of HMG-CoA and are useful in the treatment or prevention of hypercholesterolaemia, hyperlipoproteinaemia and arteriosclerosis.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

1 3-Carboxy-2-hydroxy-propane-phosphonic acid derivatives.

2
3 Coronary heart disease (CHD) is a major cause of death
4 and disability in the Western World. Epidemiological
5 evidence strongly indicates that hypercholesterol-
6 aemia - or more accurately, elevated levels of low-
7 density lipoprotein cholesterol (LDL-C) - is a major
8 risk factor for the development of CHD. Most
9 cholesterol is synthesised de novo in the human body,
10 in a multi-step process starting with acetyl-coenzyme
11 A. The rate limiting step on this pathway is regulated
12 by the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A
13 reductase (HMG-CoA reductase) which catalyses the
14 conversion of HMG-CoA to mevalonic acid. The enzyme is
15 therefore a prime target for pharmacological interven-
16 tion for the control of hypercholesterolaemia.

17
18 The present invention relates to novel 4-phosphono-3-
19 hydroxy butanoic acid derivatives which inhibit the
20 action of 3-hydroxy-3-methylglutaryl-coenzyme A
21 reductase (HMG CoA reductase) and as such are useful in
22 inhibiting cholesterol biosynthesis, and also relates
23 to hypercholesterolemic compositions containing these
24 compounds.

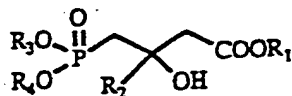
25
26 FR-A-2596393 (Sanofi SA) discloses 3-carboxy-2-
27 hydroxy-propane-phosphonic acid derivatives including
28 salts thereof which are useful as hypolipaeic agents
29 and have the formula:

30

31

32

33



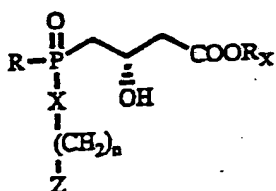
wherein

R_1 and R_2 = H, lower alkyl or optionally substituted aryl or arylalkyl;

R_3 and R_4 = H, lower alkyl or optionally substituted aryl or arylalkyl.

These compounds are reported to give greater reduction in cholesterol, triglyceride and phospholipid levels than meglutol.

DE-A-3817375 and US-A-4904646 (Squibb) disclose other 3-carboxy-2-hydroxy phosphonic acid derivatives and salts thereof as hypercholesterolemic agents having the formula:



1 wherein

2

3 R_x is H, or alkyl;

4

5 R is OH, lower alkoxy or lower alkyl;

6

6 n is 1 or 2;

7

8 X is O, NH or CH_2 ,

9

10 Z is a hydrophobic anchor, specifically an
11 optionally substituted aryl, an optionally
12 substituted naphthyl, or a decalin radical of
13 general formula:

14

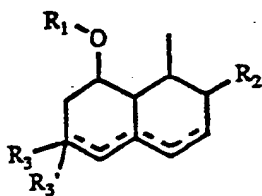
15

16

17

18

19



20

21

22

23

24

R_1 = optionally substituted ester or ether

25

26

R_2 = lower alkyl

27

28

R_3, R_3' = independently H, OH, lower alkyl,
alkylaryl, aryl.

29

30

31 No biological data is given describing the potency of
32 these compounds. Compounds containing an R_3 alkenyl
33 substituent are not described or claimed in these

1 documents.

2

3 Our copending application WO-A-9100280 discloses
4 hypercholesterolemic agents of formula:

5

6

7

8

9

10

11

12

13

14

15

wherein

16

17

R_1 is alkyl, alkylaryl or aryl;

18

19

R_2 is H or lower alkyl;

20

21

R_3 is C_{2-6} alkenyl optionally substituted with an
22 optionally substituted aryl moiety;

23

24

R_4 is H, lower alkyl, a pharmaceutically
25 acceptable salt or an internal δ -lactone;

26

27

a, b, c and d are single or double bonds except
28 that when a or c is double then b is single.

29

30

31

32

33

This document discloses that introduction of certain R_3
alkenyl substituents increases the HMG CoA reductase-
inhibitory activity of these compounds relative to
mevinolin in which R_3 is methyl.

1 Compounds which incorporate both R_3 alkenyl
2 substituents on the decalin and a phosphonyl group in
3 the glutaryl-like side-chain are new. The present
4 invention provides these novel decalin-based compounds
5 which are potent inhibitors of the enzyme 3-hydroxy-3-
6 methylglutaryl coenzyme A (HMG-CoA) reductase and
7 therefore are useful in the treatment or prevention of
8 hypercholesterolaemia, hyperlipoproteinaemia and
9 arteriosclerosis, particularly atherosclerosis.

10

11 According to the first aspect of the invention, there
12 is provided a compound of general formula I

13

14

15

16

17

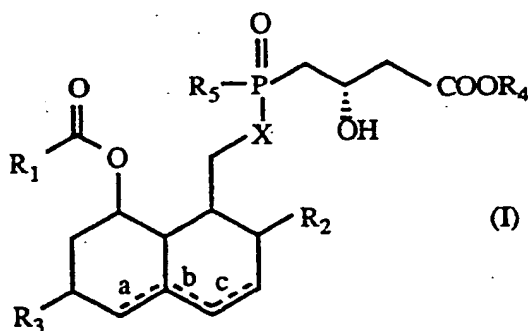
18

19

20

21

22



23

24 wherein

25

26 R_1 represents a C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-8})alkyl,
27 C_{2-8} alkenyl, optionally C_{1-6} alkyl substituted phenyl, or
optionally substituted phenyl(C_{1-6} alkyl) group;

28

29 R_2 represents C_{1-8} alkyl group;

30

31 R_3 represents a C_{2-6} alkenyl group or a C_{2-6}
32 alkenyl group linked to an optionally substituted
33 phenyl group;

1 R_4 represents a hydrogen atom, a C_{1-5} alkyl group,
2 or a C_{1-5} alkyl group substituted with a group
3 chosen from optionally substituted phenyl,
4 dimethylamino or acetylamino or a group M;

5
6 R_5 represents a hydroxyl, -OM, or a C_{1-8} alkoxy
7 group;

8
9 M represents a cation capable of forming a
10 pharmaceutically acceptable salt;

11
12 X represents an oxygen atom, NH group or CH_2
13 group;

14
15 a, b and c represent independently single or
16 double bonds except that when a or c are double
17 bonds then b represents a single bond;

18
19 or a pharmaceutically or veterinarily acceptable acid
20 addition salt or hydrate thereof.

21
22 As used herein, the term " C_{1-8} alkyl" refers to
23 straight chain or branched chain hydrocarbon groups
24 having from one to eight carbon atoms. Illustrative of
25 such alkyl groups are methyl, ethyl, propyl, isopropyl,
26 butyl, isobutyl, sec-butyl, tert-butyl, pentyl,
27 neopentyl, hexyl, heptyl and octyl.

28
29 As used herein, the term " C_{1-5} alkyl" refers to a
30 straight chain or branched chain hydrocarbon group
31 having from one to five carbon atoms. Illustrative of
32 such groups are methyl, ethyl, propyl, isopropyl,
33 butyl, isobutyl, sec-butyl, tert-butyl and pentyl.

1 As used herein, the term "C₁₋₆ alkyl" refers to a
2 straight chain or branched chain hydrocarbon group
3 having from one to six carbon atoms. Illustrative of
4 such groups are methyl, ethyl, propyl, isopropyl,
5 butyl, isobutyl, sec-butyl, tert-butyl, pentyl and
6 hexyl.

7
8 As used herein, the term C₂₋₈ alkenyl refers to
9 straight chain or branched chain hydrocarbon groups
10 having from two to eight carbon atoms and having in
11 addition one or more double bonds, of either E or Z
12 stereochemistry where applicable. This term would
13 include for example vinyl, (E)-prop-1-enyl,
14 (Z)-prop-1-enyl, but-3-enyl, (E)-1-methylpent-1-enyl,
15 5-hexenyl and oct-7-enyl.

16
17 The term "C₂₋₆ alkenyl" refers to a straight chain or
18 branched chain hydrocarbon moiety having two to six
19 carbon atoms and possessing an E or Z double bond.
20 This includes for example, vinyl, (E)-prop-1-enyl,
21 (Z)-prop-1-enyl, but-3-enyl, (E)-1-methylpent-1-enyl,
22 and 5-hexenyl. Cognate terms (such as "C₂₋₆" alkenoxy)
23 are to be construed accordingly.

24
25 The term "C₃₋₈ cycloalkyl" refers to a saturated
26 alicyclic moiety having from 3 to 8 carbons arranged in
27 a ring and includes, for example, cyclopropyl, cyclo-
28 butyl, cyclopentyl, and cyclooctyl.

29
30 The term "optionally substituted phenyl group" means
31 substituted with up to four substituents each of which
32 may be C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, thiol, amino,
33 halo, (including fluoro, chloro, bromo, and iodo),

1 trifluoromethyl or nitro.

2

3 As used herein, the term "C₁₋₆ alkoxy" refers to
4 straight chain or branched chain alkoxy groups having
5 from one to six carbon atoms. Illustrative of such
6 alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy,
7 butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy,
8 neopentoxy and hexoxy.

9

10 The phrase "a pharmaceutically acceptable salt" as used
11 herein and in the claims is intended to include
12 non-toxic alkali metal salts such as sodium, potassium,
13 calcium and magnesium, the ammonium salt and salts with
14 non-toxic amines such as trialkylamines, dibenzylamine,
15 and other amines which have been or can be used to form
16 salts of carboxylic and phosphonic acids.

17

18 In compounds of this invention, the presence of several
19 asymmetric carbon atoms gives rise to diastereoisomers,
20 each of which consists of two enantiomers, with the
21 appropriate R or S stereochemistry at each chiral
22 centre. The invention is understood to include all
23 such diastereoisomers, their optically active
24 enantiomers and mixtures thereof. The phosphorus atom
25 forms an additional chiral centre and the invention
26 includes both diastereoisomers at the phosphorus atom.

27

28 Disregarding any asymmetric centres which might be
29 present in substituents R₁₋₆, the preferred relative
30 and absolute stereochemistry is as shown in the
31 structure below. The Cahn, Ingold, Prelog designations
32 for this compound are 1S, 2S 4aR, 6S, 8S, 8aS, and 3'S.
33 Both diastereomers at phosphorus are equally preferred.

1 It should be noted that the preferred diastereomers of
2 other compounds of the invention may differ in their
3 R-S designations because of the manner in which the
4 sequence rules are determined.

5

6

7

8

9

10

11

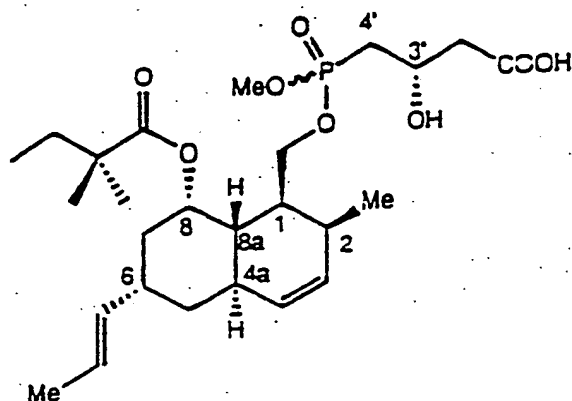
12

13

14

15

16



17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

Clearly in compounds in which a or b (in the general formula) are double bonds, the carbon atom labelled C_{4a} will not be an asymmetric centre.

Preferred compounds include those in which independently or in any combination:

R₁ represents a C₁₋₅ branched chain alkyl group;

R₂ represents methyl or ethyl;

R₃ is E-1-propenyl;

R₅ represents a hydroxy or a C₁₋₅ alkoxy group;

c or a and c are double bonds;

1 X is oxygen or an NH group.

2

3 Examples of this preferred group are:

4

5 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
6 octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-
7 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]
8 phosphonyl-3'-hydroxybutanoic acid;

9

10 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
11 octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-
12 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy](R and
13 S) methoxyphosphonyl-3'-hydroxybutanoic acid;

14

15 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
16 octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-
17 6-[(E)-prop-1-enyl]-1-naphthalenyl)methylenamino]
18 phosphonyl-3'-hydroxybutanoic acid,

19

20 or salts, particularly lithium salts, thereof.

21

22 Compounds of general formula I may be prepared by any
23 suitable method known in the art and/or by the
24 following process, which itself forms part of the
25 invention.

26

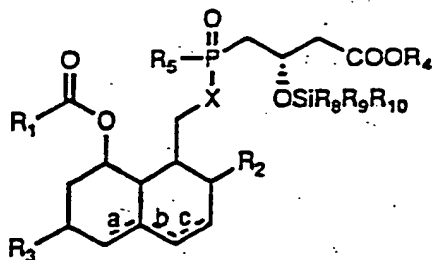
27 According to a second aspect of the invention, there is
28 provided a process for preparing a compound of general
29 formula I as defined above, the process comprising:

30

31 (a) deprotecting a compound of general formula II

32

33



II

wherein,

R_1 , R_2 , R_3 , R_4 , R_5 , X , a , b and c are as defined for general formula I; and

R_8 , R_9 and R_{10} independently comprise C_{1-8} alkyl or phenyl;

using a nucleophilic desilylating agent;

(b) optionally after step (a), converting a compound of general formula I to another compound of general formula I.

Examples of suitable nucleophilic reagents for use in step (a) are sources of fluoride ions such as tetrabutylammonium fluoride in an inert solvent such as tetrahydrofuran and hydrofluoric acid in aqueous acetonitrile. With both these reagents, the reaction is preferably carried out at ambient temperature and when tetrabutylammonium fluoride is used as the

1 reagent, the reaction should be carried out in an inert
2 atmosphere, for example nitrogen or argon and in the
3 presence of an organic acid buffer such as acetic acid.
4 However, other methods for the removal of silyl
5 protecting groups are known and any of these may also
6 be used.

7
8 A compound of general formula I in which either or both
9 R_4 or R_5 is an alkyl group can be converted to a
10 compound in which both R_4 and R_5 are hydrogen atoms by
11 hydrolysis using at least a 2-fold excess of a base.
12 Any base can be used but hydroxylic bases such as
13 lithium, sodium or potassium hydroxides or metal alkyl
14 thiolates such as lithium or sodium methyl thiolate or
15 sodium phenyl thiolate are particularly suitable.

16
17 The reaction temperature may be from 50°C to 80°C and
18 any solvent may be used which boils at a temperature at
19 least as high as the required reaction temperature and
20 which dissolves both the starting material and the
21 base. Suitable solvents include polar organic solvents
22 such as methanol, ethanol, tetrahydrofuran,
23 acetonitrile, N,N-dimethylformamide, alone or mixed with
24 water, or water itself. The hydrolysis is allowed to
25 continue for at least twelve hours.

26
27 Compounds of general formula I in which both R_4 and R_5
28 are alkyl groups can be selectively hydrolysed to give
29 compounds of general formula I in which R_4 is a
30 hydrogen atom and R_5 is an alkyl group by mild
31 hydrolysis with one of the bases mentioned above,
32 although in this case, there should not be an excess
33 amount of base. The polar organic solvents mentioned

1 above are also suitable for this mild hydrolysis
 2 reaction but the reaction temperature should be between
 3 0°C and 50°C, preferably ambient temperature. The
 4 reaction proceeds to completion in about twelve hours.

5

6 Silyl ethers of general formula II wherein X is O or NH
 7 can be prepared by reaction of a compound of general
 8 formula III

9

10

11

12

13

14

15

16

17

18

19

20 wherein

21

22 X is O or NH and

23

24 R₁, R₂, R₃, a, b and c are as defined in general
 25 formula I; with a compound of general formula IV

26

27

28

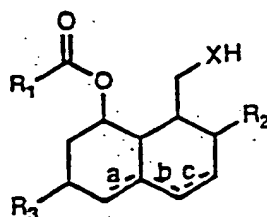
29

30

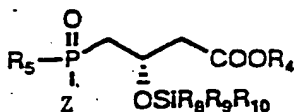
31

32

33 wherein R₄ and R₅ are as defined in general formula I;



III



IV

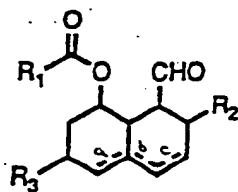
1 R_8 , R_9 and R_{10} are as defined in general formula II;
2 and
3

4 Z is hydroxy, fluoro, chloro or bromo.
5

6 When Z is fluoro, chloro or bromo, the reaction should
7 be carried out under an inert atmosphere, for example
8 nitrogen or argon, preferably at ambient temperature.
9 The solvent for this reaction is preferably inert and
10 basic, for example pyridine, but inert non-basic
11 organic solvents such as dichloromethane or
12 tetrahydrofuran may also be used although in this case,
13 a mild organic base such as triethylamine or N-methyl
14 morpholine must also be present.
15

16 When Z is a hydroxy group, the compounds of general
17 formula II may be prepared by reaction of compounds of
18 general formulae III and IV together with a condensing
19 agent, for example dicyclohexanecarbodiimide (DCC) or
20 water soluble derivatives thereof. In this case, the
21 reaction should preferably be carried out in an inert
22 solvent such as dichloromethane, tetrahydrofuran or
23 pyridine. In place of DCC, it is possible to use other
24 condensing agents such as carbonyldiimidazole.
25

26 Compounds of general formula IV are known and can be
27 prepared by the method described in DE-A-3817375.
28 Compounds of general formula III in which X is O are
29 known and compounds of general formula III wherein X is
30 NH can be prepared from compounds of general formula V
31
32
33



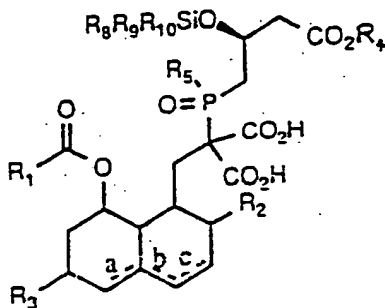
V

wherein R_1 , R_2 , R_3 , a , b and c are as defined for general formula I;

by the method described in DE-A-3817375.

Compounds of general formula V are also known.

Compounds of general formula II wherein X is CH_2 can be prepared by decarboxylation of compounds of general formula VI



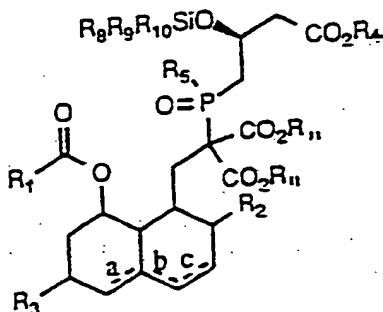
VI

wherein

1 a, b, c, R₁, R₂, R₃, R₄, R₈, R₉, and R₁₀ are as defined
 2 above and R₅ is a C₁₋₈ alkoxy group.

3
 4 The decarboxylation reaction may be performed by any
 5 method known in the art, but preferred methods include
 6 heating a compound of general formula VI to a
 7 temperature of greater than 70°C in an inert,
 8 non-basic, relatively high-boiling solvent such as
 9 water, DMSO or DMF. The solvent may optionally contain
 10 ionic solutes for example alkali metal halides (eg
 11 sodium chloride in DMSO) or sodium bicarbonate (in DMF)
 12 which are known to promote decarboxylation reactions.

13
 14 Compounds of general formula VI can be obtained by
 15 hydrolysis of compounds of general formula VII



VII

24
 25 wherein

26
 27 a, b, c, R, R₁, R₂, R₃, R₄, R₈, R₉ and R₁₀ are as
 28 defined above;

29
 30 R₅ is a C₁₋₈ alkoxy group; and

31
 32 each R₁₁ independently represents a hydrogen atom, a
 33 C₁₋₅ alkyl (optionally substituted phenyl) group or the

1 two R_{11} groups may, together with the atoms to which
2 they are attached, form a C_{6-8} cyclic system, for
3 example an isopropylidene diester as in mel drums acid.

4
5 For the hydrolysis, any combination of base and solvent
6 that is suitable for the hydrolysis of esters may be
7 used, but preferred systems include lithium, sodium or
8 potassium hydroxides or metal alkyl thiolates such as
9 lithium or sodium methylthiolates or sodium phenyl
10 thiolate. The reaction may be performed in a solvent
11 which dissolves both the base and the substrate. Polar
12 organic solvents are suitable for this purpose for
13 example methanol, ethanol, THF, acetonitrile, DMF or
14 DMSO, alone or mixed with water or water itself.
15 Optionally if R_{11} is an acid sensitive grouping such as
16 a t-butyl ester, then acid hydrolysis methods such as
17 are known in the art may be employed.

18

19 Compounds of general formula VII can be obtained by
20 reaction of a compound of general formula VIII

21

22

23

24

25

26

27

28

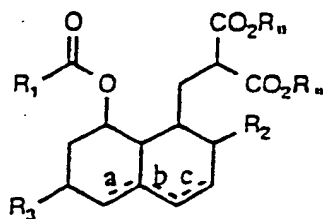
29

30 wherein

31

32 a, b, c, R_1 , R_2 , R_3 and R_{11} are as defined above;

33



VIII

1 with a compound of general formula X

2

3

4

5

6

7

8

9

10

11 wherein

12

13 R_4 , R_8 , R_9 and R_{10} are as defined above;

14

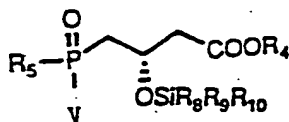
15 R_5 is a C_{1-8} alkoxy group;

16

17 V is fluoro, chloro or bromo.

18

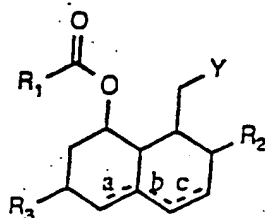
19 The reaction may be performed by addition of a strong
 20 non-nucleophilic base to a compound of general formula
 21 VIII in a polar aprotic solvent between -78°C and
 22 ambient temperature to deprotonate the compound at a
 23 position alpha to the carboxylic ester groups. Once
 24 the malonate anion has been formed, a solution of a
 25 compound of general formula X in the same solvent is
 26 added to it between 0°C and ambient temperature, and
 27 the reaction mixture is heated at between 50 and 100°C
 28 until the reaction is complete. Suitable bases for the
 29 first step include sodium alkyl lithium reagents,
 30 sodium and potassium hydride, secondary alkyl lithium
 31 amides such as lithium diisopropyl amide and sodium and
 32 lithium hexamethyl disilazides. THF, dimethoxyethyl
 33 ether, DMF and DMSO are preferred solvents for this



X

1 transformation although other solvents could also be
2 used. Compounds of general formula X can be prepared
3 by methods described in DE-A-3817375.

4
5 Compounds of general formula VIII can be prepared from
6 compounds of general formula IX



IX

7
8
9
10
11
12
13
14
15
16 wherein a, b, c, R₁, R₂ and R₃ are as defined in
17 general formula I and Y is a leaving group, for example
18 a chloride, bromine, or iodine atom, or a mesylate,
19 tosylate or triflate group;

20
21 by reaction with an equivalent, or preferably an
22 excess, of the anion of a malonic acid derivative in a
23 suitable non-protic solvent.

24
25 The malonic acid derivative can be a monoalkyl-, or
26 dialkyl- or arylester of malonic acid, and cyclic
27 diesters such as Meldrum's acid are also suitable.
28 Lower alkyl diesters such as dimethyl and diethyl
29 malonate lower alkyl monoesters such as monomethyl-,
30 monoethyl- and mono-t-butyl- malonic acid are preferred
31 since these reagents react more quickly and in higher
32 yield.

33

1 The reaction is performed by addition of a strong
2 non-nucleophilic base to a solution of the malonate
3 compound in a non-protic solvent. For diesters, one
4 equivalent of base to each equivalent of malonate
5 compound should be used, but for monoesters of malonic
6 acid, two equivalents of base for each equivalent of
7 substrate should be employed. The deprotonation may be
8 performed between -78°C and room temperature. Any base
9 and solvent suitable for the deprotonation of compound
10 VIII may be used for this step, although
11 hexamethyldisilazide in THF is especially preferred.
12 The reaction proceeds by adding a solution of a
13 compound of general formula IX to a solution of the
14 malonate anion in the same solvent and the reaction
15 mixture is heated at between 50 and 100°C for at least
16 5 hours.

17
18 Compounds of general formula IX can be prepared from
19 known compounds of general formula III where X is
20 oxygen. Mesylates, tosylates and triflates of general
21 formula IX may be prepared directly from alcohols of
22 general formula III by reaction with the requisite
23 sulphonyl chloride in a basic organic solvent such as
24 pyridine or a non-protic solvent such as
25 dichloromethane containing a mild organic base such as
26 triethylamine at or below 0°C . Such transformations
27 are known in the art. Halides of general formula IX
28 may be prepared from these sulphonate esters by
29 reactions also known in the art. For example an iodide
30 of general formula IX may be prepared from the mesylate
31 by heating it under reflux in methyl ethyl ketone
32 containing 5 equivalents of sodium iodide for 18 hours.

33

1 Compounds of general formula II are valuable
2 intermediates in the preparation of compounds of
3 general formula I and therefore according to a third
4 aspect of the invention, there is provided a compound
5 of general formula II.

6
7 The compounds of general formula I are useful as anti-
8 hypercholesterolaemic agents for the treatment of
9 arteriosclerosis, hyperlipidaemia, familial hyperchol-
10 esterolaemia and like diseases in humans. The
11 invention therefore also relates to a method for the
12 treatment of patients suffering from these diseases.

13
14 According to a further aspect of the invention there is
15 provided a compound of general formula I for use in
16 human or veterinary medicine, particularly in the
17 treatment or prophylaxis of hypercholesterolaemia,
18 hyperlipidaemia or arteriosclerosis.

19
20 According to yet a further aspect of the invention,
21 there is provided the use of a compound of general
22 formula I in the preparation of an agent for the
23 treatment or prophylaxis of hypocholesterolaemia,
24 hyperlipidaemia or arteriosclerosis.

25
26 Compounds of general formula I may be administered
27 orally or parenterally in the form of a capsule, a
28 tablet, an injectable preparation or the like. It is
29 usually desirable to use the oral route. Doses may be
30 varied, depending on the age, severity, body weight and
31 other conditions of human patients but daily dosage for
32 adults is within a range of from about 2 mg to 2000 mg
33 (preferably 5 to 100 mg) which may be given in one to

1 four divided doses. Higher doses may be favourably
2 employed as required.

3
4 The compounds of this invention may also be
5 co-administered with pharmaceutically acceptable non
6 toxic cationic polymers capable of binding bile acids
7 in a non-reabsorbable form in the gastrointestinal
8 tract. Examples of such polymers include
9 cholestyramine, colestipol and
10 poly[methyl-(3-trimethylaminopropyl)-iminotrimethylene
11 dihalide]. The relative amounts of the compounds of
12 this invention and these polymers is between 1:100 and
13 1:15000.

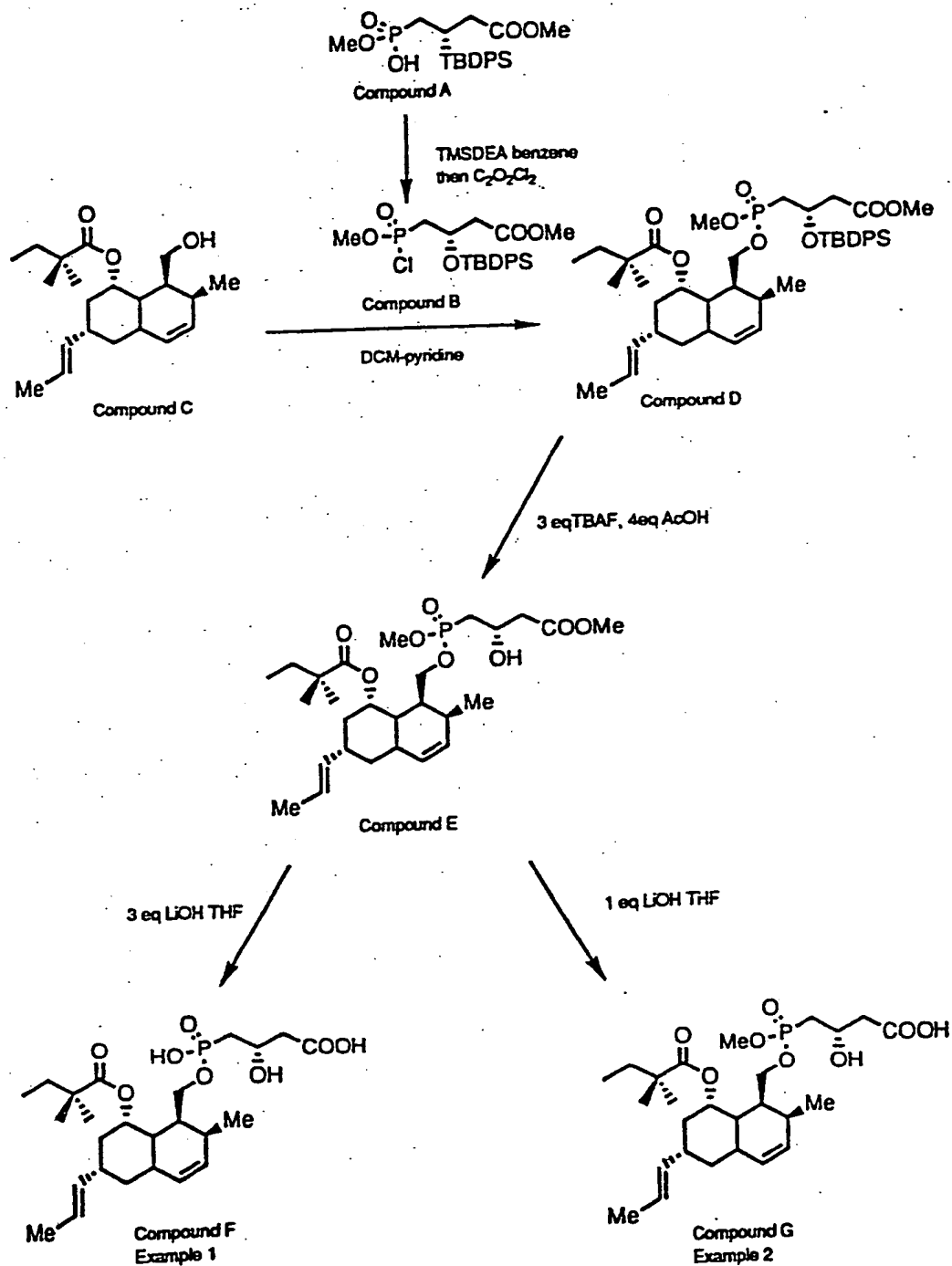
14
15 The following examples show representative compounds
16 encompassed by this invention and their syntheses (see
17 Scheme 1). However, it should be understood that they
18 are for the purposes of illustration only.

19
20 Organic solutions were dried over sodium sulphate or
21 magnesium sulphate, and evaporated under reduced
22 pressure. NMR spectra were recorded at ambient
23 temperature in deuteriochloroform at 250 MHz for proton
24 and 62.5 MHz for carbon unless noted otherwise. All
25 chemical shifts are given in parts per million relative
26 to tetramethylsilane. Infra red spectra were recorded
27 at ambient temperature in solution in chloroform, or in
28 the solid state in a potassium bromide disc as noted.

29
30 Chromatography was carried out using Woelm 32-60 μ m
31 silica.

32
33

Scheme 1



Example 1Step A

Methyl-(S)-3[1,1-dimethylethyl]-diphenylsilyloxy]-4-
(chloromethoxyphosphinyl)-butanoate.
[compound B]

A stirred solution of methyl-(S)-3[(1,1-Dimethylethyl)-diphenylsilyloxy]-4-(hydroxymethoxyphosphinyl)-butanoate [compound A] (1.16 g, 2.56 mmol) (prepared by the method of DE-A-3817375) in 1:1 dry benzene (5 ml) and dichloromethane (5ml) was treated with trimethylsilyldiethylamine (1.16 ml, 6.1 mmol) at room temperature under argon. After 1 hr the solvent was evaporated under reduced pressure and the residue taken up in dichloromethane (5ml) containing 2 drops of DMF. The solution was cooled to -15°C and treated with oxalyl chloride (292 µl, 3.34 mmol). After 5 min at -15°C, the solution was allowed to warm to room temperature over 1 hr and then evaporated under reduced pressure to give crude methyl-(S)-3[1,1-dimethylethyl]-diphenylsilyloxy]-4-(chloromethoxyphosphinyl)-butanoate [compound B] (1.10 g) as a yellow oil.

Step B

Methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-
6[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]methoxy-
phosphinyl-3'[1,1-dimethylethyl]-diphenylsilyloxy]-
butanoate.
[compound D]

Crude phosphinyl chloride [compound B] (234mg, 0.496 mmol) was added in three portions of 115, 60 and 60mg

1 after 0, 15 and 40 hr respectively, to a stirred
2 solution of (1S,2S,4aR,6S,8S,8aS)(1,2,4a,5,6,7,8,8a
3 octahydro-2-methyl-8-[(2"-dimethyl-1"oxo-butyl)-oxy]-6-
4 [(E)-prop-1-enyl]-1-naphthalenyl)methanol [compound C]
5 (50 mg, 0.149 mmol) (prepared by the method of patent
6 WO-A-9100280) in 2:1 pyridine-dichloromethane (0.5 ml)
7 at room temperature under argon. After 3 days the
8 reaction mixture was diluted with dichloromethane (25
9 ml) and washed twice with 3N citric acid solution (2x20
10 ml). Drying over MgSO₄ and evaporation under reduced
11 pressure gave a clear oil (240 mg) which was flash
12 chromatographed on silica (8 g) under gradient elution
13 [1:4 ethyl acetate-hexane to 2:3 ethyl acetate-hexane]
14 to afford methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,
15 4a,5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-
16 1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)
17 methyleneoxy]methoxy-phosphinyl-3'[1,1-dimethylethyl)-
18 diphenylsilyloxy]-butanoate [compound D] (37 mg, 0.052
19 mmol, 35% yield) as an oil.

20

21 TLC 40% ethyl acetate-hexane R_f = 0.25 U.V. and PMA.

22

23

24 Step C

25 Methyl-4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2, 4a,
26 5,6,7,8,8a octahydro-2-methyl-8-[(2"-dimethyl-
27 1"oxobutyl)-oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl)
28 methyleneoxy]methoxyphosphinyl-3'-hydroxy-butanoate.
29 [compound E]

30

31 The silyl ether [compound D] (74 mg, 0.096 mmol) was
32 stirred for 18hr at room temperature under argon in a
33 solution of dry THF (1.2 ml) containing tetrabutyl-

1 ammonium fluoride (0.29 mmol) and acetic acid (0.38
2 mmol). The reaction mixture was diluted with diethyl
3 ether (20 ml) and washed with water (20 ml) then
4 saturated sodium carbonate solution (20 ml) and dried
5 over MgSO₄. Flash chromatography of the concentrated
6 residue using 1:1 ethyl acetate-hexane increasing to
7 ethyl acetate gave the title compound as an oil.

8
9 Yield (29 mg, 0.055 mmol) 61%

10

11 TLC Ethyl acetate R_f 0.38

12

13 δ H (CDCl₃) 0.84(3H, t, J 7.3 Hz); 0.94(3H, d, J 6.4
14 Hz); 1.16(6H, 2s); 1.17-2.17(14H, m); 3.71(3H total - 2
15 isomers at phosphorus, 2d, J 10.9 Hz); 3.73-4.4(7H, m);
16 5.6-5.8(2H, m).

17

18 δ C (CDCl₃) 176.8, 176.2, 134.6, 130.9, 121.6, 68.0,
19 63.4, 62.8, 51.3, 42 approx, 41.5, 38.1, 36.4, 36.3,
20 35.8, 34.5, 33.8, 31.5, 29.9, 29.7, 29.5, 23.2, 16.5,
21 14.3, 14.0, 11.1, 7.8.

22

23 Example 2

24

25 4'-[1S,2S,4aR,6S,8S,8aS,3'S,](1,2,4a,5,6,7,
26 8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-
27 oxyl-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy]-
28 phosphonyl-3'-hydroxy-butanoic acid.

29 [compound F]

30

31 Compound E from Example 1 (14.5 mg, 2.9×10^{-5} M) was
32 heated at 50°C for 16 hr with three equivalents of
33 lithium hydroxide (2 mg, 8.7×10^{-5} M) in THF (1.1 ml).

1 The crude reaction mixture was chromatographed on two
2 analytical 1mm kieselgel 60 plates (elution with 7:3
3 isopropanol- $\text{NH}_4\text{OH}_{\text{aq}}$) to give the title compound as an
4 oil (7 mg, $1.4 \times 10^{-5}\text{M}$).

5

6 Yield 48%.

7

8 TLC eluant 7:3 i-PrOH: $\text{NH}_4\text{OH}_{\text{aq}}$ $R_f = 0.51$ U.V. only.

9

10 δH (CDCl_3) 0.95(6H, s); 1.2-2.1(19H, m); 3.8(1H, m);
11 4.4(3H, m); 5.05-5.8(5H, m).

12

13 Example 3

14

15 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,
16 8,8a octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-
17 oxy]-6-[(E)-prop-1-enyl]-1-naphthalenyl) methyleneoxy]-
18 R and S-methoxyphosphinyl-3'-hydroxybutanoic acid.
19 [compound G]

20

21 Compound E from Example 1 (14.5 mg, $2.7 \times 10^{-5}\text{M}$ was
22 stirred for 16 hr in tetrahydrofuran (0.4 ml)
23 containing 1.2 equivalents of lithium hydroxide ($3.5 \times$
24 10^{-5}M). The neat solution was thin-layer
25 chromatographed on two 10 x 20 cm Kieselgel 60
26 analytical plates eluting with 7:3 isopropanol-2N
27 aqueous ammonia solution to give the desired compound
28 as an oil (13 mg, $2.5 \times 10^{-5}\text{M}$).

29

30 Yield 93%.

31

32 TLC eluant 7:3 i-PrOH: $\text{NH}_4\text{OH}_{\text{aq}}$ R_f 0.68.

33

1 δ H (CDCl₃) 0.84(3H, t, J 7.3Hz); 0.94(3H, d, J 6.4Hz);
2 1.16(6H, 2s); 1.17-2.17(14H, m); 2.5(4H, m); 3.71(3H
3 total, 2d, J 10.9Hz for each POME); 3.73-4.4(7H, m);
4 5.60-5.8(2H, m).

5
6 δ C (CDCl₃) 176.8, 176.2, 134.6, 130.9, 121.6, 68.0,
7 63.4, 62.8, 51.3, 42 approx, 41.5, 38.1, 36.4, 36.3,
8 35.8, 34.5, 33.8, 31.5, 29.9, 29.7, 29.5, 23.2, 16.5,
9 14.3, 14.0, 11.1, 7.8.

10
11 The intrinsic HMG-CoA reductase inhibition activity of
12 the claimed compounds is measured in the in vitro
13 protocols described below.

14
15 Example 4 - Pharmacology

16
17 IN VITRO DETERMINATION OF INHIBITORY POTENTIAL OF
18 HMG-CoA REDUCTASE INHIBITORS.

19
20 HMG-CoA reductase was induced in rats by feeding a
21 normal diet supplement with 3% cholestyramine resin for
22 one week prior to sacrifice. The livers were excised
23 from the sacrificed rats and microsomal pellets
24 prepared by the method of Kleinsek et al, Proc. Natl.
25 Acad. Sci. USA, 74 (4), pp 1431-1435, 1977. Briefly,
26 the livers were immediately placed in ice-cold buffer I
27 (see below) and homogenised in a Potter-Elvehjem type
28 glass/TEFLON homogeniser (10 passes at 1000 rpm). (The
29 word TEFLON is a trade mark). The homogenate was
30 centrifuged at 100,000 x g for 75 minutes, the
31 microsomal pellet resuspended in buffer II (see below)
32 and centrifuged at 100,000 x g for 75 minutes. The
33 resultant pellet was stored at -70°C until required for

1 assay purposes. The compositions of buffers I and II
2 are given below.

3
4
5 Buffer I

6 50 mM KPO₄ pH 7.0

7 0.2 M sucrose

8 2 mM DTT

Buffer II

50 mM KPO₄ pH 7.0

0.2 M sucrose

2mM DTT

50 mM EDTA

10
11
12 Assay of HMG-CoA Reductase Activity and Determination
13 of Activity of Inhibitors

14
15 Membrane bound enzyme isolated as above is used for
16 determining the activity of inhibitors. The assay is
17 performed in a total volume of 300 µL in 100 mM KPO₄ pH
18 7.2 buffer, containing 3 mM MgCl₂, 5 mM glucose-6-
19 phosphate, 10 mM reduced glutathione, 1 mM NADP, 1 unit
20 glucose-6-phosphate dehydrogenase, and 1 mg/mL BSA,
21 with resuspended enzyme. Putative inhibitors are
22 dissolved in dimethylsulphoxide and 10 µL aliquots
23 added to the incubation.

24
25 The assay is pre-incubated at 37°C for 10 minutes and
26 initiated by the addition of 0.1 µCi 3-hydroxy-3-
27 methyl-[3-¹⁴C]glutaryl coenzyme A (52 Ci/Mole) followed
28 by incubating the complete reaction at 37°C for 10
29 minutes. At the end of this period the reaction is
30 stopped by adding 300 µL of a 10 mM mevalonolactone
31 solution in 0.1 M hydrochloric acid and the mevalonic
32 acid product allowed to lactonise for a further period
33 of 30 minutes. The product is then isolated by

1 chromatography using Bio-Rex 5 resin and the enzyme
2 activity quantified by liquid scintillation spectro-
3 photometry.

4
5 Appropriate controls are included in the assay and IC_{50}
6 values obtained by graphical means.

7
8 Representative IC_{50} values for compounds F and G in the
9 isolated enzyme assay were 11 and 2900 nanomoles
10 respectively. In this assay, the IC_{50} value for
11 dihydromevinolin was 30 nanomoles.

12
13 Included within the scope of this invention is the
14 method of treating arteriosclerosis, familial hyper-
15 cholesterolaemia or hyperlipidaemia which comprises
16 administering to a subject in need of such treatment a
17 non toxic therapeutically effective amount of the
18 compounds of formulae I or II or pharmaceutical
19 compositions thereof.

20

21

22

23

24

25

26

27

28

29

30

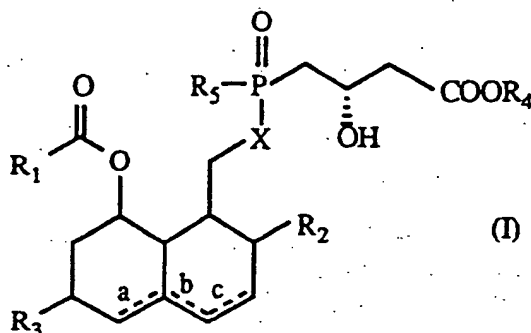
31

32

33

CLAIMS

1. A compound of general formula I:



wherein

R_1 represents a C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl(C_{1-8})alkyl, C_{2-8} alkenyl, optionally C_{1-6} alkyl substituted phenyl, or optionally substituted phenyl(C_{1-6} alkyl) group;

R_2 represents C_{1-8} alkyl group;

R_3 represents a C_{2-6} alkenyl group or a C_{2-6} alkenyl group linked to an optionally substituted phenyl group;

R_4 represents a hydrogen atom, a C_{1-5} alkyl group, a C_{1-5} alkyl group substituted with a group chosen from optionally substituted phenyl, dimethyl amino or acetylamino; or a group M;

R_5 represents a hydroxyl, -OM, or C_{1-8} alkoxy group;

1 M represents a cation capable of forming a
2 pharmaceutically acceptable salt;

3
4 X represents an oxygen atom, NH group or CH₂
5 group;

6
7 a, b and c represent independently single or
8 double bonds except that when a or c are double
9 bonds then b represents a single bond;

10
11 or a pharmaceutically or veterinarily acceptable acid
12 addition salt or hydrate thereof.

13
14 2. A compound as claimed in claim 1 wherein R₁ is a
15 C₁₋₅ branched chain alkyl group.

16
17 3. A compound as claimed in claim 1 or claim 2
18 wherein R₂ is a methyl or an ethyl group.

19
20 4. A compound as claimed in any one of claims 1 to 3
21 wherein R₃ is E-1-propenyl.

22
23 5. A compound as claimed in any one of claims 1 to 4
24 wherein R₅ is a hydroxy or a C₁₋₅ alkoxy group.

25
26 6. A compound as claimed in any one of claims 1 to 5
27 wherein c or a and c are double bonds.

28
29 7. A compound as claimed in any one of claims 1 to 6
30 wherein X is oxygen or an NH group.

31
32 8. 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
33 octahydro-2-methyl-8-[(2"-dimethyl-1"oxobutyl)-oxy]-6-

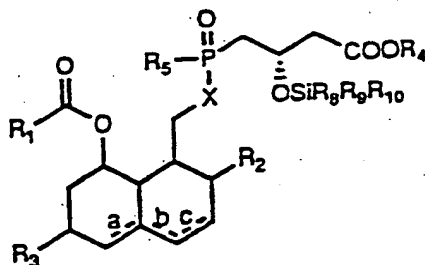
1 [(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy]phos-
 2 phonyl-3'-hydroxybutanoic acid;

3
 4 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
 5 octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-
 6 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleneoxy](R and
 7 S) methoxyphosphonyl-3'-hydroxybutanoic acid; or

8
 9 4'-[(1S,2S,4aR,6S,8S,8aS,3'S,)(1,2,4a,5,6,7,8,8a
 10 octahydro-2-methyl-8-[(2"-dimethyl-1"-oxobutyl)-oxy]-
 11 6-[(E)-prop-1-enyl]-1-naphthalenyl)methyleamino]
 12 phosphonyl-3'-hydroxybutanoic acid.

13
 14 9. A process for the preparation of a compound as
 15 claimed in any one of claims 1 to 8, the process
 16 comprising

17
 18 (a) deprotecting a compound of general formula II



II

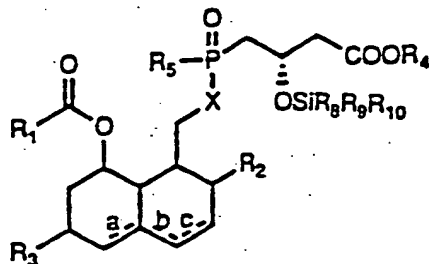
30 wherein

31
 32 R₁, R₂, R₃, R₄, R₅ and X are as defined in claim 1; and

33

- 1 R_8 , R_9 and R_{10} independently comprise C_{1-8} alkyl or
2 phenyl;
3
4 with a nucleophilic desilylating agent;
5
6 (b) optionally after step (a) converting a compound of
7 general formula I to another compound of general
8 formula I.
9
10 10. A process as claimed in claim 9 wherein the
11 nucleophilic deprotecting agent comprises a source of
12 fluoride ions, for example tetrabutylammonium fluoride
13 or hydrofluoric acid.
14
15 11. A compound as claimed in any one of claims 1 to 8
16 for use in medicine.
17
18 12. The use of a compound as claimed in any one of
19 claims 1 to 7 in the preparation of an agent for the
20 treatment or prophylaxis of hypocholesterolemia,
21 hyperlipidaemia or arteriosclerosis.
22
23 13. A pharmaceutical or veterinary composition
24 comprising a compound as claimed in any one of claims 1
25 to 8 together with a pharmaceutically or verterinarily
26 acceptable excipient.
27
28 14. A composition as claimed in claim 13 further
29 including at least one pharmaceutically acceptable
30 non-toxic cationic polymer capable of binding bile
31 acids in a non-reabsorbable form in the
32 gastrointestinal tract.
33

1 15. A compound of general formula II



II

15 wherein R_1 , R_2 , R_3 , R_4 , R_5 and X are as defined in
16 claim 1; and

17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

15 R_8 , R_9 and R_{10} independently comprise C_{1-8} alkyl or
16 phenyl.